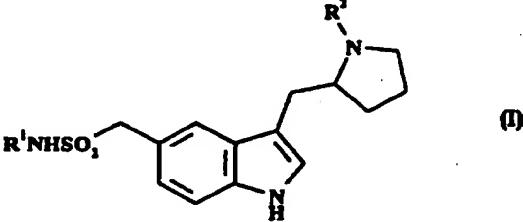


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |  |  |   |
|--|--|--|---|
| (51) International Patent Classification <sup>6</sup> :<br><b>A61K 31/40</b>   |  | A2   | (11) International Publication Number: <b>WO 96/11685</b><br>(43) International Publication Date: <b>25 April 1996 (25.04.96)</b> |
| (21) International Application Number: <b>PCT/EP95/03965</b>   |  | (22) International Filing Date: <b>5 October 1995 (05.10.95)</b>   |   |
| (30) Priority Data:<br><b>9420529.1 12 October 1994 (12.10.94) GB</b>  |  | (23) Extent of Protection:<br><b>GB</b>  |   |
| (71) Applicant (for GB only): <b>PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).</b>  |  | (24) Agents: <b>HAYLES, James, Richard et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).</b>                                   |   |
| (71) Applicant (for all designated States except GB JP US): <b>PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V.S.A. [BE/IE]; Latouche House, International Financial Centre, Dublin 1 (IE).</b>   |  | (81) Designated States: <b>AU, CA, CN, CZ, FI, HU, JP, KR, MX, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b> |   |
| (71) Applicant (for JP only): <b>PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</b>   |  | (25) Publication Date: <b>25 April 1996 (25.04.96)</b>   |   |
| (72) Inventors; and  |  | (26) Priority Data:  |   |
| (73) Inventors/Applicants (for US only): <b>GUPTA, Paul [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). LAHUERTA, Juan [ES/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). JONES, Shirley [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). ROBSON, Susan, Frances [GB/GB]; Pfizer Central Research, Ramsgate</b>   |  | (27) Description of Drawings:  |   |
| (54) Title: <b>USE OF INDOLE DERIVATIVES FOR THE TREATMENT OF DERMATOLOGICAL DISORDERS PERIPHERAL NEUROPATHIES, ARTHRITIS, HEADACHE, OROFACIAL PAIN, ALLERGIC OR CHRONIC OBSTRUCTIVE AIRWAYS DISEASE, GLAUCOMA AND OCULAR INFLAMMATION</b>   |  |  |   |
| (57) Abstract  |  |  |   |
| <p>The invention provides the use of a compound of formula (I) wherein R<sup>1</sup> and R<sup>2</sup> independently represent H or C<sub>1</sub>-C<sub>6</sub> alkyl, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of: dermatological disorders; peripheral neuropathies; arthritis; gastrointestinal or urogenital diseases; headache associated with substances or their withdrawal; tension headache; pediatric migraine; post-traumatic dysautonomic cephalgia; orofacial pain; allergic or chronic obstructive airways diseases; glaucoma or ocular inflammation; or prophylaxis of migraine.</p> |  |  |   |
|    |  |  |   |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |                          |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria                  | GB | United Kingdom                           | MR | Mauritania               |
| AU | Australia                | GE | Georgia                                  | MW | Malawi                   |
| BB | Barbados                 | GN | Guinea                                   | NE | Niger                    |
| BE | Belgium                  | GR | Greece                                   | NL | Netherlands              |
| BF | Burkina Faso             | HU | Hungary                                  | NO | Norway                   |
| BG | Bulgaria                 | IE | Ireland                                  | NZ | New Zealand              |
| BJ | Benin                    | IT | Italy                                    | PL | Poland                   |
| BR | Brazil                   | JP | Japan                                    | PT | Portugal                 |
| BY | Belarus                  | KE | Kenya                                    | RO | Romania                  |
| CA | Canada                   | KG | Kyrgyzstan                               | RU | Russian Federation       |
| CF | Central African Republic | KP | Democratic People's Republic<br>of Korea | SD | Sudan                    |
| CG | Congo                    | KR | Republic of Korea                        | SE | Sweden                   |
| CH | Switzerland              | KZ | Kazakhstan                               | SI | Slovenia                 |
| CI | Côte d'Ivoire            | LI | Liechtenstein                            | SK | Slovakia                 |
| CM | Cameroun                 | LK | Sri Lanka                                | SN | Senegal                  |
| CN | China                    | LU | Luxembourg                               | TD | Chad                     |
| CS | Czechoslovakia           | LV | Latvia                                   | TG | Togo                     |
| CZ | Czech Republic           | MC | Monaco                                   | TJ | Tajikistan               |
| DE | Germany                  | MD | Republic of Moldova                      | TT | Trinidad and Tobago      |
| DK | Denmark                  | MG | Madagascar                               | UA | Ukraine                  |
| ES | Spain                    | ML | Mali                                     | US | United States of America |
| FI | Finland                  | MN | Mongolia                                 | UZ | Uzbekistan               |
| FR | France                   |    |  | VN | Viet Nam                 |
| GA | Gabon                    |    |  |    |                          |

**New method of treatment**

This invention relates to new uses of certain indole derivatives in the treatment or prophylaxis of medical disorders.

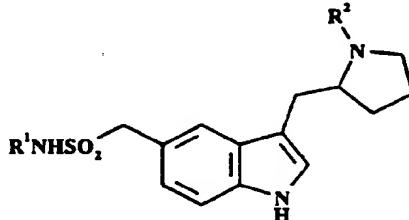
5

International Patent Application WO 92/06973 discloses a series of indole derivatives which are potent serotonin (5-HT) agonists. These compounds are useful for treating disorders arising from deficient serotonergic neurotransmission comprising hypertension, depression, anxiety, eating disorders, obesity, drug abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania and headache associated with vascular disorders. The compounds covered by WO 92/06973 include (R)-5-(methylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole (Example 5A, known as CP-122,288) and (R)-5-(methylaminosulphonylmethyl)-3-(pyrrolidin-2-ylmethyl)-1H-indole (Example 6A, known as CP-122,638).

It is known that CP-122,288 and CP-122,638 exhibit potency against neurogenic inflammation in dura mater [W.S. Lee and M.A. Moskowitz, Brain Research, 626 (1993), 303-305].

20

It has now been found that compounds of formula I,



wherein R<sup>1</sup> and R<sup>2</sup> independently represent H or C<sub>1</sub>-C<sub>6</sub> alkyl, and their pharmaceutically acceptable salts, are useful in a considerable number of conditions.

25 These include:

(a) dermatological disorders, such as psoriasis; eczema; atopic eczematous dermatitis; pruritis (also known as intractable itch) including itch associated with liver cirrhosis, cancer and haemodialysis; burns; scalds; sunburn; insect bites;

urticaria; and sweat gland abnormalities; bullous pemphigoid; photo-dermatoses; skin blisters; adult acne; chicken pox; and dermatitis herpetiformis;

(b) peripheral neuropathies including postherpetic neuralgia, diabetic neuropathies such as peripheral polyneuropathy and radiculopathy; causalgia and reflex sympathetic dystrophy; post-mastectomy neuralgia; post-surgical neuralgia and pain; vulvar vestibulitis; phantom limb pain; thalamic syndrome (central post-stroke pain); temporo mandibular joint syndrome; metatarsalgia (Morton's neuralgia); and neurogenic pain from nerve compression caused, for example, by a prolapsed intervertebral disc or carpal and tarsal tunnel syndromes;

10 (c) arthritis, including osteoarthritis and rheumatoid arthritis; systemic lupus erythematosus; fibromyalgia; ankylosing spondilitis; and tendinitis;

(d) gastrointestinal and urogenital diseases, including cystitis; gastroesophageal reflux; gastritis; urge continence; inflammatory bowel disease; irritable bowel syndrome; the compounds are also effective in regulating gastrointestinal tract motility;

15 (e) headache associated with substances or their withdrawal (e.g. drug withdrawal); tension headache; paediatric migraine; prophylaxis of migraine; and post-traumatic dysautonomic cephalgia;

(f) orofacial pain including toothache and pain of dental origin; earache; TMJ

20 pain (temporal mandibular joint pain); sinus pain; myofacial pain; non-arthritic and non-musculoskeletal cervical pain; mouth ulcers; Menière's disease; and atypical facial neuralgia;

(g) allergic and chronic obstructive airways diseases including rhinitis; conjunctivitis; bronchial oedema; bronchial asthma; neurological pulmonary oedema (adult

25 respiratory disease syndrome); anaphylaxis; and angioedema;

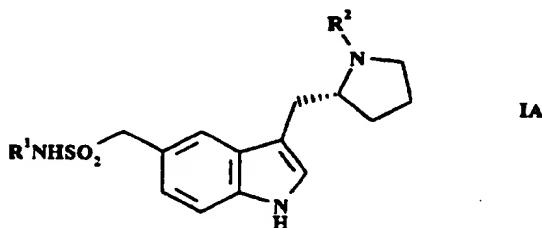
(h) glaucoma (also known as intra-ocular pressure) and ocular inflammation.

Thus, one aspect of the invention relates to the use of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in any one of the above-mentioned conditions.

Another aspect of the invention relates to a pharmaceutical formulation comprising a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, characterized in that the formulation is adapted for administration to the skin. As mentioned below, conventional methods may be used to prepare the topical formulation. The formulation may be adapted for administration to the skin to the exclusion of other routes of administration.

Yet another aspect relates to a method of use in any one of the above-mentioned 10 conditions which comprises administering a therapeutically effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

The compounds of formula I, as defined above, may exist as optical isomers. The 15 invention includes all optical isomers and mixtures thereof. However, compounds of formula I having (R)-stereochemistry as shown in formula IA,



are preferred.

20 Alkyl groups which R<sup>1</sup> and R<sup>2</sup> may represent can be linear, cyclic or branched. However, it is preferred that R<sup>1</sup> and R<sup>2</sup> each represent methyl. Compounds of formula I include CP-122,288, CP-122,638 and (R)-5-(aminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole.

25 The action of the compounds of formula I in preventing or alleviating the conditions mentioned above is unexpected. Some of these conditions may be treated using capsaicin [(E)-N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-6-nonenamide] which is known to antagonise neurogenic inflammation by depleting

neuropeptide levels from neurones. However, the mode of action of capsaicin is totally different from that of the compounds of formula I. When administered to a patient, capsaicin selectively activates primary sensory afferents to cause the release of substances known as "SP" (substance P) and "CGRP" (calcitonin gene related peptide) which cause inflammation. The continued action of capsaicin results in the depletion of neuropeptides from the primary sensory afferents, so that these nerves lose their capacity to promote tissue inflammation. Thus, the initial action of capsaicin is generally to cause intense itching and other effects associated with neurogenic inflammation. In contrast, the compounds of formula I above suppress inflammation immediately by activating an inhibitory receptor located at the sensory nerve ending. Given this difference in function, the effects of the compounds of formula I cannot be predicted from the known effects of capsaicin; furthermore, they do not have the undesirable effects caused by the initial inflammation experienced when capsaicin is administered.

15

Pharmaceutically acceptable salts of the compounds of formula I include non-toxic acid addition salts, that is salts containing pharmacologically acceptable anions. Particular salts are mentioned in WO 92/06973, which also describes methods of preparing the compounds mentioned above and formulations containing the 20 compounds for administration to patients. However, at least for oral administration, the fumarate salt is preferred.

The compounds of formula I and their salts defined above may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. 25 Thus the active compounds may be formulated for topical, oral, buccal, intranasal, parenteral (e.g. intravenous, intramuscular or subcutaneous) or rectal administration, or in a form suitable for inhalation or insufflation. Formulation methods are described in the above-mentioned Patent Application WO 92/06973.

30 The daily dose of the compound administered to a patient for treatment of the above-mentioned conditions will be determined by a physician for any given patient but in general it will be typically 0.1 - 200mg of active ingredient per unit

oral, parenteral or buccal dose which could be administered, for example, 1 to 4 times daily for an adult weighing 70kg). In an aerosol formulation each metered dose or "puff" may contain from 20 $\mu$ g to 1000 $\mu$ g of the compound and the overall daily dose will be from 100 $\mu$ g to 10mg. However, it has been found that compounds CP-122,288 and CP-122,638 and (R)-5-(aminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole are active at doses several orders of magnitude less. The typical unit dose for topical, oral, buccal, intranasal, parenteral (e.g. intravenous, intramuscular or subcutaneous), rectal, inhalation or insufflation administration will then be 1 nanogram - 200mg for these compounds with a correspondingly reduced dose for aerosol formulations.

The following tests are believed to give an indication of a test compound's efficacy in the majority of the conditions mentioned above:

- 15 (i) The effect of compounds of the invention in suppressing inflammation may be demonstrated by the method of Escott and Brain (*Br. J. Pharmacol.* (1993), 110, 772-776) in which oedema in the rat hind paw is measured after saphenous nerve stimulation. The test compound is administered intravenously at different amounts and the results are recorded as the ratio of plasma extravasation in the stimulated/unstimulated hind paw. It is found that compound CP 122,288 has a significant effect at administered amounts as low as  $2 \times 10^{-14}$  mol/kg [Kajekar, *Br. J. Pharmacol.* (1995), 115, 1-2].
- 20 (ii) The effect of a compound of the invention in suppressing vasodilation may be demonstrated by the method of Kajekar *et al* [*Br. J. Pharmacol.* (1995), 115, 8P] in which vasodilation in the rat hind paw is measured after saphenous nerve stimulation. The test compound is administered intravenously at different doses and the results are recorded as the change in the increase in skin blood flow. It is found that CP-122,288 has a significant effect at doses as low as  $2 \times 10^{-12}$  mol/kg.
- 25 30 The invention is illustrated by the following examples.

Example 1

Topical aqueous cream formulation

| Ingredient  | Quantity (g) |
|---|--------------|
| (R)-5-(methylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole fumarate | 0.001g       |
| Aqueous Cream BP  | 999.999g     |

1kg of Aqueous Cream BP contains emulsifying ointment (300g), phenoxyethanol (10g) and purified water (690g). 1kg of emulsifying ointment contains emulsifying wax (300g), white soft paraffin (500g) and liquid paraffin (200g).

Example 2Topical oily cream formulation

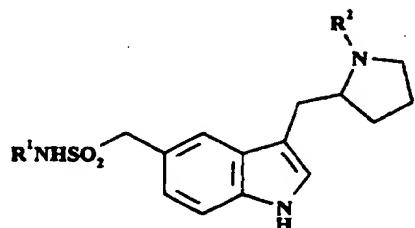
10

| Ingredient  | Quantity (g) |
|---|--------------|
| (R)-5-(methylaminosulphonylmethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole fumarate | 0.001g       |
| Oily Cream BP   | 999.999g     |

1kg of Oily Cream BP contains wool alcohols ointment (500g), phenoxyethanol (10g), dried magnesium sulphate (5g) and purified water (485g). 1kg of wool alcohols ointment contains wool alcohols (60g), hard paraffin (240g), white soft paraffin (100g) and liquid paraffin (600g).

**Claims:**

## 1. Use of a compound of formula I,



5 wherein  $\text{R}^1$  and  $\text{R}^2$  independently represent H or  $\text{C}_1\text{-C}_6$  alkyl, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of dermatological disorders.

2. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of peripheral neuropathies.

10 3. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of arthritis.

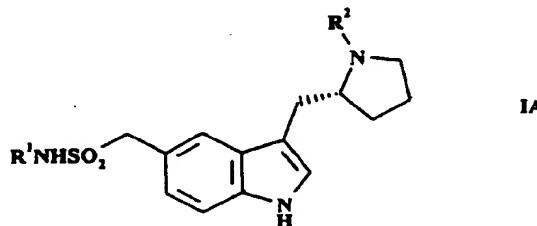
4. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of 15 gastrointestinal or urogenital diseases.

5. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of headache associated with substances or their withdrawal; tension headache; 20 paediatric migraine; post-traumatic dysautonomic cephalgia; or prophylaxis of migraine.

6. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of orofacial pain.

25 7. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of allergic or chronic obstructive airways diseases.

8. Use of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of glaucoma or ocular inflammation.
9. The use as claimed in any one of claims 1 to 8, wherein R<sup>1</sup> and R<sup>2</sup> each 5 represent methyl.
10. The use as claimed in any one of the preceding claims, wherein the compound of formula I is in the form of its fumarate salt.
11. The use as claimed in claim 1, wherein the medicament is for the treatment of pruritis.
- 10 12. The use as claimed in any one of the preceding claims, wherein the compound of formula I has (R)-stereochemistry as shown in formula IA,



13. A pharmaceutical formulation comprising a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with 15 a pharmaceutically acceptable adjuvant, diluent or carrier, characterized in that the formulation is adapted for administration to the skin.
14. A method of treatment of:
  - (a) dermatological disorders;
  - (b) peripheral neuropathies;
  - 20 (c) arthritis;
  - (d) gastrointestinal or urogenital diseases;
  - (e) headache associated with substances or their withdrawal; tension headache; paediatric migraine; post-traumatic dysautonomic cephalgia; or prophylaxis of migraine;
  - 25 (f) orofacial pain;
  - (g) allergic or chronic obstructive airways diseases; or
  - (h) glaucoma or ocular inflammation;

which comprises administering a therapeutically effective amount of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment or prophylaxis.